Magnetic Resonance Imaging Predictors for Disability in Multiple Sclerosis

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Chapter 1

General Introduction

Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic progressive disease of the central nervous system that is characterized by inflammation and neurodegeneration. It is the most common demyelinating disease in the western world and affects mainly young adults in the age between 20 and 40 years old. There is a female predominance with a female to male ratio of about 2:1. The incidence and prevalence vary worldwide but in Europe the incidence is about 4.3 per 100,000 and a prevalence of 83 per 100,000.[1] For the Netherlands the most recent data on incidence and prevalence date from 1994.[2] Estimated prevalence is 55 per 100,000 for men and 113 per 100,000 for women.

Histopathologically, MS consists of multiple focal areas of demyelination in the white and grey matter throughout the central nervous system (CNS). Both within and outside these lesions there is axonal loss and gliosis. These histopathological abnormalities vary in severity between patients, but ultimately result in multiple sclerotic plaques, characterizing the disease.[3]

The disease can manifest itself in various ways, symptoms may include motor symptoms like muscle weakness, sensory problems, ataxia, cognitive problems and many others.[4] Although the disease course is highly variable, in most patients (80%), it starts with Relapsing-Remitting MS (RRMS): with alternating periods of clinical disability (relapses) and remission.[5] In the early years of the disease most patients (almost) fully recover from the relapses but at longer follow-up (FU) some neurological deficits remain. A majority (60-70%) of patients that initially have an RRMS disease course eventually develop Secondary Progressive MS (SPMS).[6] In this phase of the disease there is a more gradual decline in clinical status altough relapses can still occur. Only about 10 to 20% of patients never experience relapses and show progressive deterioration from onset. This is the Primary Progressive MS (PPMS) disease course.[7]

Measures of disability

In an attempt to measure disability in MS, several clinical rating scales have been developed. For this thesis three different clinical rating scales were used: the Expanded Disability Status Scale (EDSS)[8], the MS Functional Composite (MSFC)[9]

and the MS Severity Scale (MSSS).[10] The EDSS was developed by Kurtzke *et al.*, and ranges from 0 (no neurological deficits) to 10 (death due to MS). It is the most widely studied clinical rating scale in MS. Despite its popularity, the EDSS is frequently criticized and other rating scales were developed in an attempt to overcome difficulties like the relative insensitivity to changes in clinical status and bias towards spinal cord pathology. This resulted in the implementation of the MSFC which is composed of 3 quantitative tests measuring walking ability, arm/hand function and cognitive function. The MSSS is based on observations of EDSS scores in large cohorts and takes disease duration into account, therewith creating a severity score (percentile) that indicates the rate of disability progression of an individual patient compared to other patients.

Treatment

Currently, there is no curative treatment available for MS. In the treatment of severe non-spontaneously recovering relapses, intravenous steroids are first choice, although not altering the long-term course of the disease.[11] For the long-term use of disease modifying therapy (DMT) in RRMS there are several options. Most frequently used are the interferons and glatiramer acetate that reduce number of relapses and slow the rate of disability progression at least in short- and medium term FU studies.[12-15] Their long-term efficacy has not yet been proved. In SPMS the effect of treatment is less clear[16], especially in the subgroup of SPMS patients without relapses there is no current effective treatment available.

Magnetic Resonance Imaging in Multiple Sclerosis

MRI is extensively used in the diagnosis and management of MS and is also used as an outcome measure in many clinical trials that evaluate the use of DMT. MS plaques appear bright on T2-weighted images and their perivenular distribution predisposes to the typical ovoid shape.[17] Sometimes they are seen as 'Dawson's fingers' at sagittal images: finger-like hyperintensities surrounding the vessels, and perpendicular to the lateral ventricles. At the time of first presentation, usually with an Clinically Isolated Syndrome (CIS), almost all patients have hyperintense

abnormalities on T2-weighted images. Most commonly affected are the corpus callosum, temporal lobes, periventricular region, infratentorial region and the juxtacortical region (Figure 1.1). In the first month(s) the T2 lesions are frequently surrounded by vasogenic edema, which resolves. Enlargement of these lesions is often seen later in the evolution, sometimes with time they also become confluent resulting in large areas with abnormal signal intensity on the T2-weighted images.[18] Most lesions that are detected on T2-weighted images are isointense on the corresponding T1-weighted images. However, in cross-sectional studies, about 20-40% of T2 lesions are hypointense to surrounding brain tissue, signal intensity ranging from mildly to strongly hypointensity.[19] These hypointense T1 lesions are known as 'black-holes'. Factors that predispose to hypointensity are prolonged disruption of the blood-brain barrier, larger lesion size and periventricular location.[19;20] Chronic hypointense T1 lesions appear infrequently in the earliest stages of the disease (CIS) and seem to be more confined to the later RRMS/SPMS stages. The contrast agent gadolinium is often used in patient management and clinical trials to detect disease activity. In active disease, there is a disruption of the blood-brain barrier. After the intravenous injection of gadolinium this disruption of the blood-brain barrier can be detected as enhancement (hyperintensity) on T1-weighted images due to leakage of gadolinium into the brain parenchyma. Type of enhancement may be either nodular or ring-shaped. Gadolinium enhancing lesions are regarded as the MRI representatives of clinical relapses. Most enhancing lesions are not clinically manifest (there is a ratio of 1:10 for relapses and number of enhancing lesions) so MRI is far more sensitive in the detection of disease activity.[21] Imaging the spinal cord might be technically more challenging than brain imaging but conventional spin-echo and several other techniques provide good quality images. At the time of the clinical diagnosis of MS, approximately 80% of patients show spinal cord abnormalities.[22] Even before the clinical diagnosis, in patients with a CIS, frequently spinal cord involvement can be shown.[23] On T2-weighted images typical focal spinal cord MS lesions are approximately one corpus vertebrae in length, sharply delineated with or without swelling of the spinal cord. Diffuse spinal cord abnormalities can be evaluated using the first echo (short time-to-echo) intermediate weighted image, on these images the spinal cord is isointense to surrounding liquor whereas pathology is hyperintense. Compared to the brain, gadolinium enhancing lesions in the spinal cord are less common.

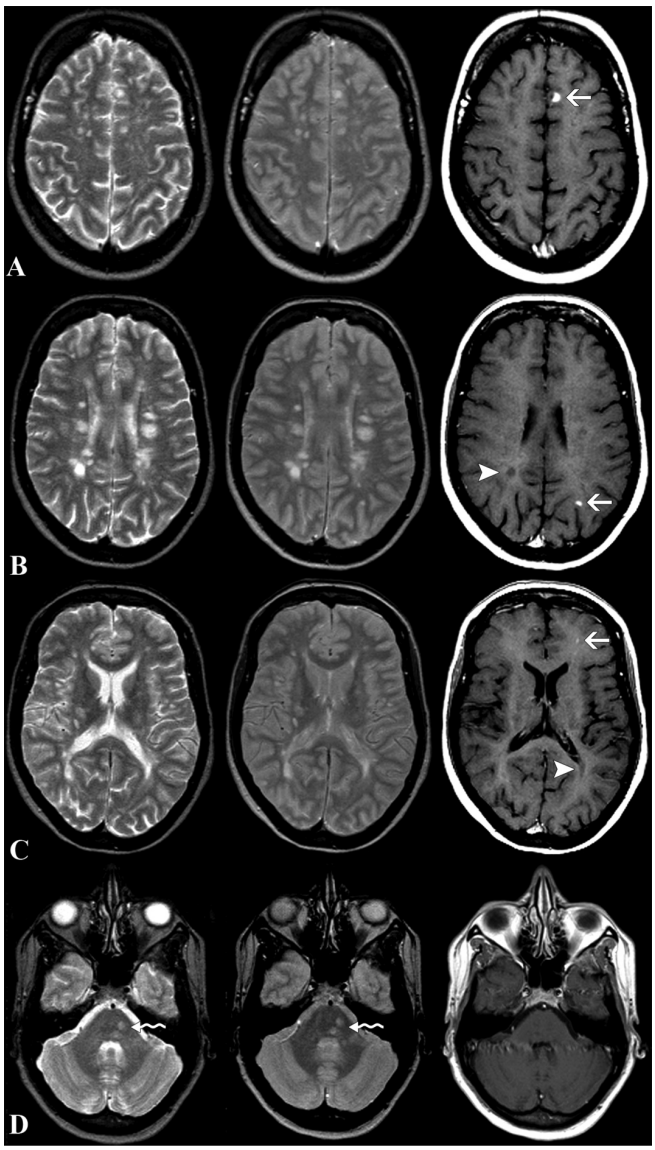


Figure 1.1. MS related abnormalities. Typical MS lesions on MR images at different levels. Displayed are T2- (left), intermediate- (middle), and gadolinium enhanced T1- (right) weighted spin-echo MR images. Multiple T2-lesions are shown, including (juxta) cortical-, periventricular-, and infratentorial lesions (waved arrow). Several T2-lesions are represented as hypointense lesions ('black holes') on the T1-weighted images (arrowheads). The T1-weighted images also show three enhancing lesions (arrows), including one (juxta) cortical lesion (arrow, row A).

Clinical and Magnetic Resonance Imaging diagnostic criteria

Even for experienced neurologists diagnosing MS may be challenging. The presence of 'dissociation in time' (two separate relapses, at least 30 days apart) and 'in space' (2 or more affected areas in the CNS) are important criteria in the diagnostic process. Classically, this was based on clinical examination and history only[24] but the most recent diagnostic criteria also incorporate paraclinical tests like Magnetic Resonance Imaging (MRI), evoked potentials and testing the cerebrospinal fluid for the presence of oligoclonal bands.[25;26]

MRI criteria for MS were developed since the late 1980's and since then there is a constant search for further improvement. Initially, the Paty criteria- four or more lesions on MRI of which at least one is located periventricularly- were commonly used.[27] Evaluation of these criteria showed high sensitivity but at the cost of a low specificity. Barkhof *et al.* formulated more stringent and robust criteria that showed higher specificity and accuracy.[28] This four-parameter dichotomized model included gadolinium enhancement, juxtacortical, periventricular and infratentorial lesions and was later modified by Tintore and colleaques (only three out of four criteria need to be fulfilled, gadolinium enhancement may be substituted by nine T2 lesions).[29] These modified criteria were then incorporated in the international MS diagnostic criteria.[25;26] At that time spinal cord lesions had gained much attention and entered the diagnostic criteria, that now state that spinal cord lesions may substitute one (modified) Barkhof criterion. More specifically, spinal cord lesions may substitute for an infratentorial brain lesion and an enhancing spinal cord lesion is considered equivalent to an enhancing brain lesion. Spinal cord lesions and brain lesions may be considered together in order to assess the total number of lesions. Imaging criteria of dissemination in space are met when there is evidence for three out of four Barkhof criteria. Imaging criteria of dissemination in time are defined by evidence of a new T2 lesion at least 1 month after the initial MRI scan or the occurrence of gadolinium enhancement at a new location at least 3 months after the initial scan. One can conclude that the diagnostic criteria for MS have evolved into a set of well structured and readily applicable criteria that provides good guidance for clinicians in diagnosing MS. Unfortunately this guidance is absent for the prediction of future disease course and disability. Prediction of disability is one of the major remaining challenges in MS-research.

Predictors for future disability

The prognosis in term of disability is highly variable between MS patients.[5;30-34] On the favorable side of this spectrum, there is a subset of patients that have a benign disease course with only few relapses and no or only minimal disability at 15 year follow-up (FU). The other side of the spectrum shows a completely different situation with rapidly progressing disability in patients that are wheelchair-bound within several years after the initial symptoms of the disease. Sometimes, even rapid progression to death due to MS (EDSS 10) is seen. The resulting uncertain future is difficult to cope with for patients but also for their treating physicians. In an attempt to limit uncertainty, predictors of disability are urgently needed. Now that DMT is available it is even more crucial to identify predictors for future disability in order to enable selection of patients that will benefit most from early treatment and protect others from receiving unnecessary treatment with related side-effects and high costs.

In long-term FU studies several clinical predictors were already identified. Probably, the strongest clinical predictor is the type of disease at onset: patients with a relapse-onset have a far more favorable prognosis compared to PPMS patients. In patients with a relapse-onset disease course short interval between onset and second relapse and disability at 2 or 5 years after onset seems to be the best predictors. High frequency of relapses also seems to be unfavorable, as is higher age at presentation and being male. Type of onset symptoms was found to be mildly predictive: compared to optic neuritis and sensory symptoms, patients presenting with pyramidal, sphincter or cerebellar symptoms, were shown to be more disabled at long-term FU.

In terms of MRI, the most frequently studied predictor for long-term disability in is T2 lesion load (T2LL). Although cross-sectional correlations between T2LL and disability are moderate in most studies and even absent in others, their role as predictor is more promising.[35] In patients with a CIS suggestive of MS, the number of T2 lesions and T2LL at baseline have been shown to predict disability at 14-year FU.[36] Several studies have indicated that the predictive value of accumulated T2LL in the first years after presentation is high and that accumulated T2LL later in the disease is less predictive for long-term disability. Since it has become clear that T2-weighted images are very sensitive for the detection of pathology but that

these T2-abnormalities are histologically a-specific there has been a search for more specific MRI predictors. Thus, attention has shifted towards T1 hypointense lesions. T1 hypointense lesions seem to reflect more severe pathology than T2 lesions and are considered measures of focal axonal loss.[37] Correlation between T1LL and disability was reported to be stronger than the correlation between T2LL and disability in several cross-sectional studies. In patients with SPMS the rate of increasing T1LL predicts increasing disability.[38]

Number of gadolinium enhancing lesions or enhancing lesion loads (GdLL) are often used as MRI measurement of clinical relapses in clinical trials testing the anti-inflammatory effects of DMT on disease activity. However, there are no studies that illustrate an important role for GdLL as predictor for long-term disability.[39]

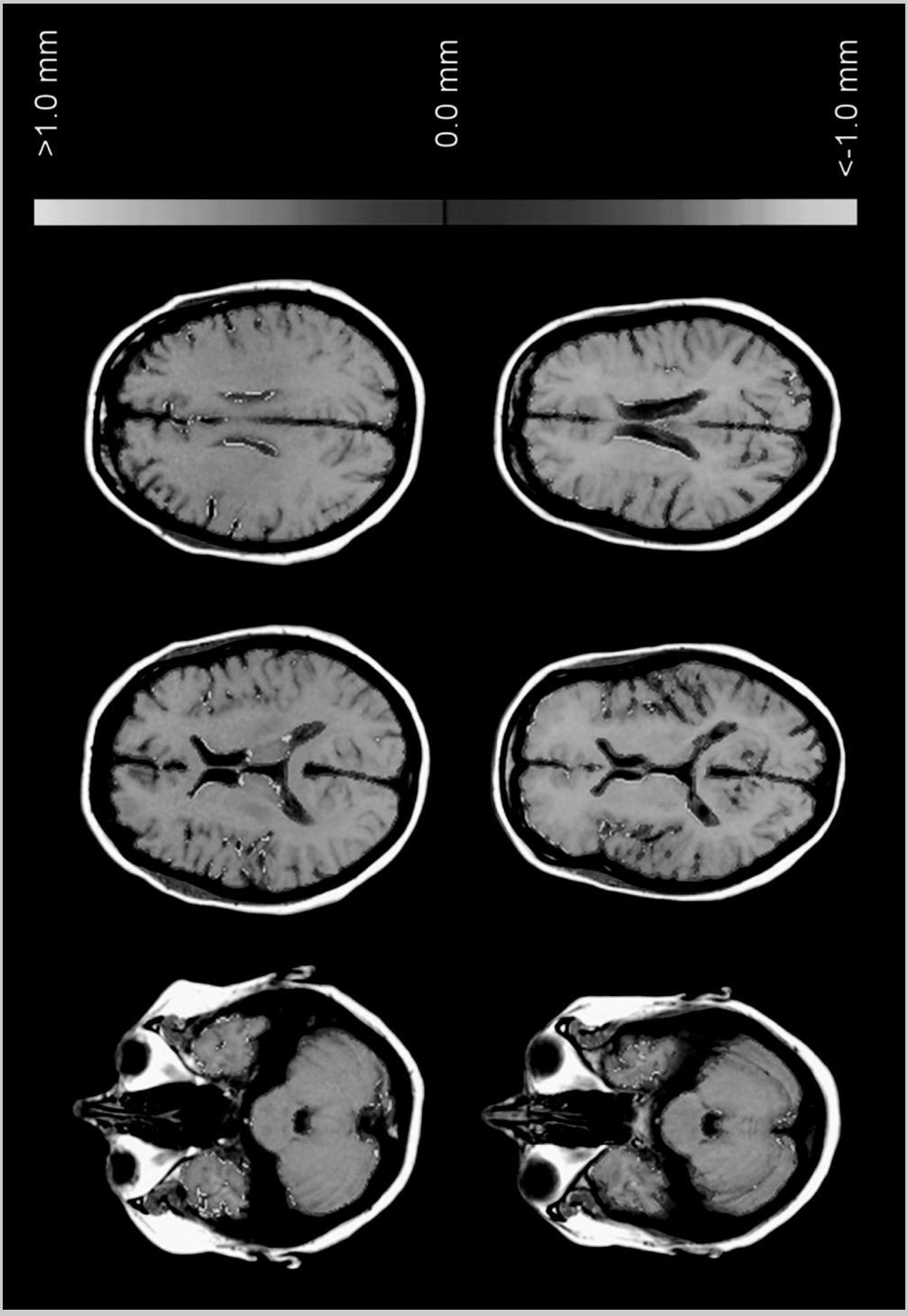
Due to the poor results of conventional lesion loads in predicting disability, research focus shifted to (rate of) cerebral atrophy. Cerebral atrophy is the conventional MRI parameter that is thought to reflect neurodegeneration most closely. The initial manual post-processing techniques were time-consuming and operator-dependent.[40] Since robust semi-automated measuring techniques became available,[41] the predictive value of cerebral atrophy measures have been studied extensively. Cerebral atrophy can be detected in patients even before the clinical diagnosis is made (in CIS suggestive of MS) and enables clear distinction from atrophy related to normal ageing. In an 8 year FU study that included RRMS patients, cerebral atrophy rate as detected in the first 2 years of the study predicted progression of disability.[42] In SPMS patients, cerebral atrophy is more outspoken than in RRMS or PPMS patients. Compared to lesion loads, cerebral atrophy seems to be a better predictor for disability in all subgroups.

Although including spinal cord MRI parameters in the study protocol seems attractive when aiming to identify MRI predictors for long-term disability, this is seldomly done. The sparse available data indicate -at best- moderate correlations in cross-sectional studies between number of focal spinal cord lesion and disability.[43;44]

Brain atrophy can be measured using several techniques. One of the most commonly used techniques for longitudinal brain atrophy assessment is SIENA (Structural Image Evaluation, using Normalization, of Atrophy). SIENA is part of the FMRIB software library (FSL), which is freely available for academic use. The first step is an automatically segmentation of the brain from the input images (typically 5mm non-enhanced T1-weighted images). In the second step the skull is estimated and a skull image is generated to be used in the registration. This is important since the skull is used as scale and skew constraint. Thirdly, the two brain images (baseline and FU) are registered (aligned) and the movement of the brain edge is fully automatic detected and calculated for the whole brain. Finally, the percentage brain volume change is calculated from the movement of all brain edge points. For cross-sectional brain atrophy assessment, SIENAX (Structural Image Evaluation, Using Normalization, of Atrophy Cross-sectional) is often used. The method is closely related to SIENA but instead, normalized brain volume is estimated from a single scan using the skull to normalize spatially to a standard image. This standard image is the Montreal Neurological Institute 152 (MNI152) standard image.

Legend to figure on page 16

Brain atrophy during 2 year FU in patients with early RRMS. Top row shows SIENA images at three different levels through the brain of a patient with low cerebral atrophy rate (percentage brain volume change (PBVC) / year was -0.3%), this patient had no progression of disability. The bottom row shows SIENA images at comparable levels in a patient with clinical progression, PBVC/year was typically higher at -2.3%. Color bar indicates brain edge movement; PBVC is calculated from the totals of the brain edge movement.



Examples of SIENA output images indicating brain edge movement

Aims and outline of the thesis

As described previously, prediction of disease progression in MS patients is very important but difficult. Several clinical and MRI predictors for long-term disability have been studied in the past but with disappointing results. The research presented in this thesis was initiated in order to further clarify the role of described predictors, combing input from radiological and clinical predictors. During this project we studied several cohorts with differing disease duration, ranging from patients with a CIS through newly clinically definite MS to well established MS. Data were derived from well documented cohorts that were followed-up prospectively. Our aims were to identify MRI predictors for long-term disability in these cohorts making use of multiparametrical models. We were specifically interested if combining predictors derived from brain and spinal cord imaging would strengthen these models. We also investigated whether or not there is an added predictive value of imaging predictors above the use of clinical predictors alone, and how much exactly MRI would add to this prediction.

In **chapter 2** the focus is on the mechanisms that are related to two of the MRI predictors we used in this thesis: T1 hypointense lesions and (rate of) cerebral atrophy. **Chapter 2.1** describes the parameters that influence patterns of enhancing lesion evolution on T1-weighted images. Also the clinical relevance of these patterns is addressed. **Chapter 2.2** gives insight to the MRI parameters related to the rate of cerebral atrophy in the first two years after the clinical diagnosis of MS. In **chapter 3** the focus is on (long-term) follow-up studies. Patients in different stages of the disease are followed-up to determine predictors for long-term disability. In **chapter 3.1** we studied a cohort of patients who were included when presenting with a CIS suggestive of MS. We describe MRI predictors derived from the baseline brain MRI scan that predict clinical relevant disability (EDSS 3) at long-term FU. **Chapter 3.2** describes a 2 year FU study of patients that were included directly after the clinical diagnosis of MS. Brain and spinal cord imaging were available at baseline and FU in this cohort. We evaluated the associations between short-term progression of disability and both MRI and clinical predictors. We also tested whether combined models (including MRI and clinical parameters) perform better than models that use clinical parameters only. The clinical FU of this cohort was extended and the 5 year FU is presented in chapter **3.3**. The study with

the longest FU is presented in chapter **3.4**. Included patients with well established MS with various disease duration were followed-up for 12 years. In this group, no spinal cord imaging was performed so only brain MRI parameters from baseline and 3 year FU MRI scan were available. Associations between MRI parameters and clinical outcome at 12 years (expressed as score on the MSSS) are described.

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